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Position Development Paper

Official Positions for FRAX® Clinical Regarding Glucocorticoids: The Impact of the Use of Glucocorticoids on the Estimate by FRAX® of the 10 Year Risk of Fracture

From Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX®

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Abstract

Given the significant impact the use of glucocorticoids can have on fracture risk independent of bone density, their use has been incorporated as one of the clinical risk factors for calculating the 10-year fracture risk in the World Health Organization's Fracture Risk Assessment Tool (FRAX®). Like the other clinical risk factors, the use of glucocorticoids is included as a dichotomous variable with use of steroids defined as past or present exposure of 3 months or more of use of a daily dose of 5 mg or more of prednisolone or equivalent. The purpose of this report is to give clinicians guidance on adjustments which should be made to the 10-year risk based on the dose, duration of use and mode of delivery of glucocorticoid preparations. A subcommittee of the International Society for Clinical Densitometry and International Osteoporosis Foundation joint Position Development Conference presented its findings to an expert panel and the following recommendations were selected. 1) There is a dose relationship between glucocorticoid use of greater than 3 months and fracture risk. The average dose exposure captured within FRAX® is likely to be a prednisone dose of 2.5–7.5 mg/day or its equivalent. Fracture probability is under-estimated when prednisone dose is greater than 7.5 mg/day and is over-estimated when the prednisone dose is less than 2.5 mg/day. 2) Frequent intermittent use of higher doses of glucocorticoids increases fracture risk. Because of the variability in dose and dosing schedule, quantification of this risk is not possible. 3) High dose inhaled glucocorticoids may be a risk factor for fracture. FRAX® may underestimate fracture probability in users of high dose inhaled glucocorticoids. 4) Appropriate glucocorticoid replacement in individuals with adrenal insufficiency has not been found to increase fracture risk. In such patients, use of glucocorticoids should not be included in FRAX® calculations.

Key Words: Glucocorticoids; fracture risk; drug-induced osteoporosis; FRAX.

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Introduction

In 1932, Cushing described the effect on bone of endogenous glucocorticoids *(1)*. In 1948, Hench and Kendall gave the first dose of compound E to a patient with rheumatoid arthritis with astounding benefit in mobility and pain *(2)*. Since that time, glucocorticoids have been used successfully in multiple clinical scenarios from hormone replacement to chronic anti-inflammatory use to high dose use for immunosuppression and prevention of transplant rejection.

It is now well recognized that the use of glucocorticoids comes with a price perhaps most noticeably on the strength and structure of bone leading to an increase in fracture risk *(2)*. Today glucocorticoid induced osteoporosis (GIOP) is the leading medication induced cause for fractures with approximately a doubling of fracture risk at any given bone mineral density (BMD). In terms of bone mass measurement, there is approximately a one standard deviation difference in equivalent fracture risks between those ever on glucocorticoids compared to a general population *(3)*. Epidemiologic studies have clearly indicated that the fracture risk imposed by glucocorticoids also occurs independently of a glucocorticoid-associated decline in BMD and therefore one needs to consider this along with other clinical risk factors in determining a patient's fracture risk.

Several randomized controlled clinical trials have demonstrated a significant reduction in fracture risk with the use of pharmacologic agents in individuals on glucocorticoids *(4,5)*. International groups have developed guidance in the use of these agents in preventing fractures in a population of glucocorticoid users *(6,7)*. It is now recommended by at least one expert panel that even low risk patients initiating glucocorticoids even at for short duration therapy be treated with pharmacologic therapy to prevent fractures *(8)*.

Recognizing this significant increased fracture risk with the use of glucocorticoids and that treatment is effective in reducing that risk, it is essential that clinicians recognize this risk and treat accordingly. One tool that has been developed to aid in combining clinical fracture risks with age and BMD is FRAX®. This Fracture Assessment Tool has been developed by the World Health Organization as a method of utilizing clinical risk factors with or without BMD to identify individuals at higher risk for fracturing. FRAX was introduced in 2008 as a website in which clinical data and BMD can be entered to determine two outcomes: 1) the ten year risk of a major osteoporotic fracture and 2) the 10 year risk of a hip fracture. The site was designed to be intuitive and easily used by primary care providers. The clinical risk factors were those that could be easily identified through history and which were largely independent of BMD in determining fracture risk. One of the clinical risk factors is the use of glucocorticoids.

In the FRAX tool, glucocorticoid use is entered as a dichotomous variable. The present version 3.1 of FRAX does not contain an explanation of glucocorticoid use. (http://www.sheffield.ac.uk/FRAX/) Previous versions explained that glucocorticoid use was defined as any past or current use of glucocorticoids at a dose of 5 mg or more for 3 months or more. (http://www.rheumatology.org/publications/hotline/03_18_flax.asp).

Inherent with simplicity comes compromise. In the case of the FRAX tool and the use of glucocorticoids, several questions can be raised about data entry and calculations. What dose of glucocorticoid produces the output in FRAX? How would the ability to change the dose within the calculations affect the output? How should clinicians adjust the 10 year risk depending on factors such as dose, length of therapy, intermittent vs. steady use, mode of delivery or effect of replacement dose? Providing guidance to help answer these questions is the purpose of this report.

Methodology & Data sources

An outline and draft of questions regarding the effect of glucocorticoid use on the out put of FRAX were developed by the steering committee. These questions were further refined by the committee following discussion within the committee of whether to recommend changes to the algorithms used in FRAX or to provide guidance for the clinician for making clinical adjustments to the output from FRAX. We selected the latter given the absence of further granularity within the studies used to develop FRAX. A literature search directed by a research librarian of PubMed, Ovid Medline and Web of Science was undertaken. Key words of the search included glucocorticoids, fractures, osteoporosis, risk factors, bone density, dose response, drug administration, Addison Disease, adrenal insufficiency, glucocorticoid insufficiency, autoimmune adrenal, autoimmune Addison. One member of the taskforce reviewed all literature accumulated and excluded those articles that were not relevant to the questions being posed. Each abstract collected was also labeled as relevant to a specific area such as general review, dose effect, effect of mode of delivery or the effect of replacement therapy on bone. Additional references were added by individual members of the committee based on their own knowledge of the literature in the field. The committee's questions, responses and rational were then reviewed by the steering committee, modified as necessary and presented to the expert panel at a joint IOF-ISCD Position Development Conference.

Statements

The following sections pose the finalized questions proposed by the committee and modified at the meeting by the Position Development Conference Expert Panel, the responses to those questions from the expert panel with grading for the quality of the evidence, the strength of the recommendation and whether these responses can be applied worldwide.

What guidance can be given to clinicians for when to include glucocorticoids as a risk in FRAX and if included as a risk, can the effect of that risk be quantified?

We explored the possibility of making recommendations that would affect the output of FRAX and discussed this with the WHO Collaborative Center. The databases that had

been used to develop FRAX were not of sufficient detail to ascertain which studies might provide adequate detail to better quantify the FRAX output (Personal communication, Eugene McCloskey). Therefore this committee recommended and the Expert Panel agreed that we should provide advice to providers for adjusting the fracture risk output. The following series of questions are designed to develop recommendations for advising clinicians in how to interpret FRAX output.

***Question*:** How does dose affect the risk of fracturing?

***Official Position*:** There is a dose relationship between glucocorticoid use of greater than 3 months and fracture risk. The average dose exposure captured within FRAX is likely to be a prednisone dose of 2.5−7.5 mg/day or its equivalent. Fracture probability is under-estimated when prednisone dose is greater than 7.5 mg/day and is over-estimated when the prednisone dose is less than 2.5 mg/day.

***Grade*:** Good, A, W

Rational

Effect of Daily Oral Dosing of Glucocorticoids on Fracture Risk

In a retrospective cohort study conducted in a general medical practice setting in the United Kingdom matched by age, sex, and medical practice of 244,235 oral glucocorticoid users and 244,235 controls, the relative rate of fractures during oral glucocorticoid treatment showed increased fracture risk (Table 1) *(10)*. Dose dependence of fracture risk was observed. Even modest doses of prednisolone therapy were associated with close to a doubling of hip fracture risk and greater risk for higher doses. For vertebral fracture, even a dose of 2.5 mg was associated with increased fracture risk and with doses greater than 7.5 mg associated with over a 5 fold risk in fracture. Fracture risks declined toward baseline rapidly after cessation of oral glucocorticoid treatment.

In a separate report, patients taking higher doses of at least 7. 5 mg daily of prednisolone or equivalent, had significantly increased risks of any fracture (1.5 fold increase), hip fracture (>2 fold increase) or vertebral fracture (>2.5 fold increase) relative to patients using oral glucocorticoids at lower doses of less than 2.5 mg per day *(11)*. Fracture risk was also elevated among people with higher cumulative exposure to oral glucocorticoids over the study period, but this effect was almost wholly removed by adjustment for daily dose, age, gender and other confounding variables.

In a 1 year study derived from data from randomized controlled trials of risedronate, van Staa et al found that statistically significant predictors of incident fracture were the baseline lumbar spine BMD and the daily glucocorticoid dose *(3)*. In the BMD threshold analysis, compared with nonusers of glucocorticoids, patients receiving glucocorticoids were younger, had a higher BMD at baseline, and had fewer prevalent fractures; nevertheless, the risk of fracture was 5.5 fold higher in the glucocorticoid users compared with nonusers. The increased risk of fracture was observed in glucocorticoid users regardless of whether osteoporosis was present. At similar levels of BMD, postmenopausal women taking glucocorticoids, as compared with nonusers of glucocorticoids, had considerably higher risks of fracture.

Table 1
Relative Increase in Fracture Risk for Use of Glucocorticoids vs. Non-Use Determined by Timing and Mode of Delivery for Any Fracture or Site-Specific Fracture

	Any	Hip	Forearm	Vertebral
RR (95% CI)				
General				
van Staa *(2)*	1.91 (1.68−2.15)	2.01 (1.74−2.29)	1.13 (0.66−1.59)	2.86 (2.56−3.16)
van Staa *(10)*	1.33 (1.29−1.38)	1.61 (1.47−0.76)	1.09 (1.01−1.17)	2.60 (2.31−2.92)
Effect of daily dose				
van Staa *(10)*				
<2.5 mg		0.99 (0.82−1.20)		1.55 (1.20−2.01)
2.5−7.5 mg		1.77 (1.55−2.02)		2.59 (2.16−3.10)
>7.5 mg		2.27 (1.94−2.66)		5.18 (4.25−6.31)
van Staa *(11)*				
>7.5 vs <2.5 mg	1.44 (1.34−1.54)	2.21 (1.85−2.64)		2.83 (2.35−2.40)
Short term				
van Staa *(14)*				
First time	1.20 (0.98−1.46)	0.86 (0.57−1.30)		2.38 (1.52−3.73)
>30 mg	1.21 (1.04−1.42)	0.78 (0.54−1.14)		1.50 (0.97−2.31)
Intermittent				
De Vries *(17)*				
Daily dose ≥30 mg, cumulative exposure >5 gm	3.63 (2.54−5.20)	3.13 (1.49−6.59)		14.42 (8.29−25.08)

In a meta-analysis of 42,542 men and women from 7 prospective trials, fracture risk was increased in those who had ever used corticosteroids. The relative risk was greater in younger individuals and for osteoporotic fractures ranged from 2.63 at age 50 to 1.71 at age 85 and for hip fractures those relative risks were 4.42 and 2.48. Sex had no effect on the relative risk figures and adjustment for BMD marginally affected the calculations. Previous fracture had no effect on these calculations *(12)*.

Recently, authors representing the WHO Collaborating Centre, made an attempt to quantify the effect of glucocorticoids on the risk of fracturing *(9)*. The authors compared the predicted risk of fracturing to the data from the United Kingdom General Research Database (GPRD) making the assumption that the average risk used in FRAX was about equivalent to the mid-range of glucocorticoid use in the GPRD of 2.5−7.5 mg daily. They concluded that for users of low dose glucocorticoids, i.e. less than 2.5 mg of prednisolone or equivalent daily, the FRAX calculated hip fracture risk should be reduced by about 30% and the major fracture risk by 20% depending on age. For doses over 7.5 mg daily the adjustment was upward for hip fractures to a 25% increase at age 40 and 50 down to 10% at age 80 and 90. For major osteoporotic fracture the increase was 20% at the younger age to again 10% at older age (see Table 2). No difference existed between sexes. Major limitations in the study were the assumption that the major osteoporotic fracture group in FRAX was equivalent to the group of non vertebral fractures in GPRD. The hip fracture data thus may be more robust. Secondly, the GPRD evaluated individuals up to 91 days after the discontinuation of glucocorticoids and thus essentially represents individuals currently taking steroids whereas FRAX asks for any use of steroids past or present. An assumption was also made that average exposure in FRAX was equivalent to the mid range of glucocorticoid use in the GPRD.

Effect of Cumulative Dose of Oral Glucocorticoids on Fracture Risk

Reductions in BMD are modestly associated with cumulative glucocorticoid exposure *(2)*. Based on a meta-analysis on the relationship between BMD changes and fractures, the changes seen in glucocorticoid users correlate with an expected 1.5 fold increase in fracture risk *(13)*.

Short Term Use of Oral Glucocorticoids on Fracture Risk

In a meta-analysis, strong correlations were found between cumulative dose and loss of bone mineral density and between daily dose and risk of fracture *(2)*. Bone loss occurred early after commencing glucocorticoid therapy and was rapid and the risk of fracture was found to increase rapidly after the start of oral glucocorticoid therapy (within 3 to 6 months) and decrease after stopping therapy. Oral glucocorticoid treatment, using more than 5 mg (of prednisolone or equivalent) daily, led to a reduction in bone mineral density and a rapid increase in the risk of fracture during the treatment period.

In a separate study using the General Practice Research Database, first-time short-term use (average glucocorticoid duration 10 days) of high-dose glucocorticoid therapy (≥30 mg) was associated with only a small increased risk of osteoporotic fracture (RR 1.21) *(17)*. In a separate group that included intermittent high-dose glucocorticoid therapy at least 3 months after the end of prior use, there was a similar small increased risk of clinical osteoporotic fractures. In addition the relative risk was 2.38 and 1.50 for clinical vertebral fractures and 0.86 and 0.78 for hip fractures, respectively for first time and the intermittent groups *(14)*.

In a double-blind, placebo-controlled, randomized study, patients with active rheumatoid arthritis starting intramuscular gold were randomly allocated to receive either prednisone or placebo *(15)*. The initial dose was 10 mg/d, which was tapered between weeks 12 and 20 with an additional 24 weeks of follow-up. Trabecular BMD in the lumbar spine as measured by quantitative computed tomography decreased 8.2% in the prednisone-treated patients between baseline and week 20. Little change was found in the placebo-treated patients, and the prednisone group had a greater mean bone loss of 9.5% than the placebo group. After discontinuation of prednisone, a mean increase was found in trabecular

Table 2
Percentage Adjustment to 10 Year Risk of Fracturing in FRAX Depending on Dose of Glucocorticoid and Age of Individual (Kanis et al With Permission, Ref. 8)

Dose	Prednisolone equivalent (mg/day)	Age			
		40,50	60,70	80,90	All ages
Hip fracture					
Low	<2.5	−40	−40	−30	−35
Medium	2.5−7.5	–	–	–	–
High	≥7.5	+25	+25/+20	+10	+20
Major osteoporotic fractures					
Low	<2.5	−20	−15/−20	−20	−20
Medium	2.5−7.5	–	–	–	–
High	≥7.5	+20	+15	+10	+15

BMD between weeks 20 and 44 of 5.3%. In both treatment groups, cortical bone mineral density did not change markedly in either period. Their findings suggest that low doses of glucocorticoids cause marked vertebral trabecular bone loss in the initial months of therapy in patients with active rheumatoid arthritis. After discontinuation of treatment, this bone loss was partially reversible.

Low dose glucocorticoids of only 5 mg daily were given in a double blind study for 6 weeks followed by a two week recovery period. Markers of both bone formation and resorption were reduced during the treatment period but showed significant reversal during recovery. The authors concluded that the effect of glucocorticoids on bone occurred at low doses and could have significant effects on bone formation and repair *(16)*.

Based on the above literature, we concluded that short term use of glucocorticoids may cause significant but in large part reversible loss of bone. The impact on fracture risk cannot be quantified and therefore a statement to the effect of such doses in FRAX cannot be made.

Past Use of Oral Glucocorticoids on Fracture Risk

In a large meta-analysis of both present and past use of corticosteroids *(12)*, there was an increased risk in both patients who had previously used and those presently on corticosteroids. Studies suggest that fracture risks decline toward baseline rapidly after cessation of oral glucocorticoid treatment *(2,18)*. Given the problems with recall bias and the apparent resolution of fracture risk on cessation of glucocorticoids, capturing past use is probably not that helpful.

***Question*:** Should intermittent use of glucocorticoids be captured by FRAX?

***Official Position*:** Frequent intermittent use of higher doses of glucocorticoids increases fracture risk. Because of the variability in dose and dosing schedule, quantification of this risk is not possible with use of the FRAX tool.

***Grade*:** Good, B, W

Rationale

Intermittent Use of Oral Glucocorticoid on Fracture Risk

The use of intermittent glucocorticoids is common; however until recently the risk of fractures associated with intermittent use had not been quantified. In a study of patients who intermittently received high-dose glucocorticoids (daily dose $\geq$15 mg) and had no or little previous exposure (cumulative exposure $\leq$1 gm) a small increased risk of osteoporotic (but not hip/femur) fracture was seen *(17)*. This risk increased substantially with increasing cumulative exposure. Among patients who received a daily dose $\geq$30 mg and whose cumulative exposure was $>$5 gm, the relative risk of osteoporotic fracture was 3.63, hip/femur fracture 3.13 and of vertebral fracture 14.42. Thus intermittent use of high-dose oral glucocorticoids may result in a small increased risk of osteoporotic fracture; however, patients who receive several courses of high-dose glucocorticoids have a substantially increased risk of fracture. However, the literature is not adequate to quantify the fracture risk.

***Question*:** Should inhaled, intranasal, topical, enteric or intravenous pulse dose be captured in FRAX?

***Official Position*:** High dose inhaled glucocorticoids may be a risk factor for fracture. FRAX may underestimate fracture probability in users of high dose inhaled glucocorticoids.

Grade: Fair, B, W

Rationale

In an effort to reduce the complications of steroid therapy, treatment is often given by topical means such as topical creams and ointments, inhaled steroids for lung disease or intranasal inhalation for rhinitis. Other uses include rectal suppositories or oral steroids with reduced absorption for inflammatory bowel disease and intravenous bolus doses for severe inflammatory disease. Whether these modes of delivery reduce the toxicity to bone associated with glucocorticoid use remains a matter of controversy.

Inhaled Glucocorticoids

By far, the largest literature on the effect of non oral glucocorticoid use exists for inhaled steroids. In the last several years a number of observational, case-controlled, nested, randomized, prospective trials and systematic reviews have been published exploring the question of the risk of fracture in patients on inhaled steroids for either COPD or asthma. Most reviews and expert opinion would suggest that inhaled doses below 800 mcg/d beclomethasone or equivalent have minimal affect on adrenal suppression or on fracture risk *(19,20)*. Three of four systematic reviews and/or meta-analyses published since 2003 have come to the conclusion that there is an association between the use of inhaled glucocorticoids and fractures *(19,21–23)*. The one study that failed to find an association included only 3 studies in the fracture portion of their review although these three trials included over 8000 patients and 195 fracture events *(24)*. In one of these reviews, a total of 43,783 cases was compared to 259,936 controls. The relative risk for non vertebral fractures was 1.12 (95% CI 1.00–1.26) per 1000 mcg increase in dose of beclomethasone dipropionate *(21)*. In another review, there were 13 studies included of which 4 were randomized trials. When the authors restricted the analysis to only users of high dose inhaled steroids, the RR of any fracture was 1.30 (95% CI 1.07, 1.58) and for hip fracture 1.32 (95% CI 0.90, 1.92) *(22)*.

DeVries et al in a case controlled study of hip fracture patients compared to controls did not find an increased risk of fracture after adjustment for underlying disease severity in adults *(25)*. Even at higher dosages, inhaled glucocorticoid use was not an independent risk factor for fracture *(25)*.

A retrospective cohort study conducted using the General Practice Research Database (GPRD) compared users of inhaled steroids to users of non steroidal medications and a control group, average ages of 45, 49 and 45 years respectively. Although the RRs of non-vertebral, hip, and vertebral fractures for the inhaled steroid treatment compared with control were 1.15 (95% CI, 1.10–1.20), 1.22 (95% CI, 1.04–1.43), and 1.51 (95% CI, 1.22–1.85), respectively, the risks did not differ significantly from those only using bronchodilators, suggesting that the excess risk may be related to the underlying respiratory disease rather than to inhaled glucocorticoid

use *(26)*. However a subsequent publication using the GPRD indicated an increased risk with an odds ratio of 1.19 95% CI, 1.10 to 1.28) after correcting for courses of oral steroid use *(27)*. This same group utilizing the Health Improvement Network Database in Great Britain, in a case controlled study, found that the fracture risk increased with increasing dose of inhaled glucocorticoids with an OR of 1.80, (95% CI 1.04−3.11) for those on mean daily dose of >1600 mcg.

In the multi-center EOLO study of 3030 individuals over age 50 with COPD, bone status was determined by quantitative ultrasound (QUS) and the presence of vertebral fractures was determined by lateral chest x-rays. Logistic regression analysis indicated that both disease severity and glucocorticoid dose, both oral and inhaled, increased vertebral fracture risk primarily in men and those at higher fracture risk by QUS *(28)*. As with other studies the highest vertebral fracture risk was associated with the highest daily dose of inhaled steroids (>1500 mcg) with an OR of 1.4 (95% CI 1.04−1.89) *(29)*.

Other Forms of Delivery

No other mode of delivery of glucocorticoids should be considered as a risk for FRAX. Very few studies have looked at other modes of delivery. Two studies looking primarily at inhaled steroids also looked at dermal topical, rectal and local use intranasal, mouth or eyes and found no increase in fracture risk for multiple routes of administration *(30)* or for nasal inhalation use alone *(31)*.

Although budesonide use in Crohn's disease may be associated with less bone loss than other oral steroids, this is not true for all studies and it is not clear that there is a benefit in reducing fractures or whether fracture risk is increased *(32,33)*.

There are no studies to suggest that the use of high dose boluses of methylprednisolone or dexamethasone lead to increased fractures and studies measuring bone density or markers of bone turnover appear to show no or minimal impact on bone *(34−37)*.

***Question*:** Should adrenal replacement effect on 10 year fracture risk be captured in FRAX?

***Official Position*:** Appropriate glucocorticoid replacement in individuals with adrenal insufficiency has not been found to increase fracture risk. In such patients, use of glucocorticoids should not be included in FRAX calculations.

***Grade*:** Fair, B, W

Rationale

A literature search was done of the topics of Addison disease, adrenal insufficiency, 21-hydroxylase deficiency and terms including osteoporosis, fractures and bone.

Replacement therapy for patients with adrenal insufficiency generally includes use of hydrocortisone, prednisone or prednisolone in 2−3 divided doses daily. If necessary, additional mineralocorticoid therapeutic effect can be added usually with fludrocortisone. In most cases replacement exceeds what would be physiologic levels of naturally occurring glucocorticoid *(38)*. This suggests that it would be likely that bone density and possibly fracture risk would be affected. Several studies have demonstrated a reduction in bone density in individuals with Addison disease *(39−41)* and with 21-hydroxylase deficiency *(42−45)* Others have not shown such an association *(46)*. Most of these studies have a small number of subjects. However, some larger studies have been published.

Lovas et al *(39)* reviewed large databases of patients with Addison's from Norway, the U.K. and New Zealand (n = 292). The authors showed significantly reduced Z-scores at both the lumbar spine and femoral neck when compared to a reference population suggesting that the recommended replacement dose of hydrocortisone of 15−25 mg daily may lead to glucocorticoid induced bone loss. Twenty-five men and women, average age 62, on adrenal replacement of either hydrocortisone 30 mg/day or prednisone 7.5 mg/day, for 21.7 ± 11.7 years, were followed with serial BMD *(47)*. Z-scores of the lumbar spine, proximal femur and ultra-distal radius were not different from manufacturer's age matched controls and no significant rate of bone loss was detected at the lumbar spine. However, 56% of the patients had T-scores below −2.5 with a greater proportion of those on prednisone. Along with the dose and type of steroid used, the duration of therapy and high cumulative dose could be a factor leading to lower bone density *(48)*. Zelissen et al were able to show that at least in men those with low bone density were receiving a higher dose of hydrocortisone measured as mg/kg body weight. After correcting for confounding factors, there was a linear relationship between dose and bone density in the lumbar spine *(49)*.

Studies of children, young adults and adult women with congenital adrenal hyperplasia (CAH) from 21-hydroxylase deficiency have low bone density *(42−45)*. In a study of 61 women, age 18−63, with CAH there was a significant decrease in bone density at the spine and femoral neck. More fractures occurred in the study population than in an equal number of age matched controls ($p < 0.001$) *(44)*. This is the only study identified that found an increase in fracture risk. The lack of fracture data may be due to the small size of most of these studies and/or the younger age of the patients in many of the studies.

In Summary

There is substantial evidence that the historically published and at least in the past, typically prescribed dose of hydrocortisone or prednisone in patients with auto-immune adrenal insufficiency or congenital adrenal hyperplasia is higher than physiologic. Although the literature is not entirely in agreement, there appears to be a reduction in bone density in these individuals although in the case of CAH, this could be related to reduced bone growth in childhood. There are insufficient data to determine if there is an increase in fracture risk. It is not known whether a replacement dose of a glucocorticoid is associated with an increased fracture risk above that predicted by BMD as is seen by therapeutic use of steroids. As such, a quantitative adjustment of the fracture risk in FRAX cannot be made. Until further information is known, the fracture risk should best be based on the bone density, age and the other clinical risk factors used in FRAX.

Additional Questions for Future Research

Despite the presence of a significant database in the published literature of studies on the effect of glucocorticoids on fracture risk, gaps remain in our ability to quantify the effect of glucocorticoids on fracture risk. Although there are data to support some estimation of risk based on glucocorticoid daily dose, there is considerably less ability to quantify the effect by the length of treatment or the mode of delivery. We would pose the following questions to help guide further investigation.

1. Although it would appear that any dose of glucocorticoid use is associated with increased fracture risk, can we better define the dose interaction with the host to develop better algorithms for safe treatment?
2. It is apparent that local use of glucocorticoids generally is safer than systemic use. Can we identify modes of delivery that are clinically free of toxicity at least to bone?
3. Can we better identify the mechanism for steroid induced bone loss to help develop agents that are less likely to increase the fracture risk?
4. What additional risk factors increase an individual's fracture risk when taking glucocorticoids?

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Appendix 1. Position Conference Members

Organizers: Didier B. Hans (Chair), Cyrus Cooper (Co-chair), Sanford Baim, Bess Dawson-Hughes, John A. Kanis, William D. Leslie, Marjorie M. Luckey, Rene Rizzoli, Catalina Poiana, John P. Bilezekian (Moderator), Socrates E. Papapoulos (Co-moderator).

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Expert Panel: John P. Bilezekian (Moderator), Socrates E. Papapoulos (Co-moderator), Jonathan D. Adachi, Robert D. Blank, Roland Chapurlat, Wu (Paulo) Chih-Hsing, Edward Czerwinski, Aldolfo Diez Perez, Hans P. Dimai, Ghada El-Hajj Fuleihan, Saeko Fujiwara, Ruxandra M. Ionescu, John A. Kanis, Mike McClung, Sergio Ragi-Eis, Jan Stepan, Kenneth G. Saag, John T. Schousboe, Wei Yu, Cristiano Zerbini.

Supporting Person: Peter D. Brown (ISCD), Patrice McKenney (IOF), Helena Johansson, Judit Nagy, Anders Oden and Denys A. Wahl.